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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,503	10/26/2005	Ali Badache	FM-07-US	4472

50446 7590 09/03/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
09/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,503	BADACHE ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 31-34* is/are pending in the application.

4a) Of the above claim(s) *17-26 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/2/05; 4/17/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-26 and 31-34 are all the pending claims for this application.

2. Claims 27-30 were canceled and new Claims 31-34 were added in the Reply of 5/12/08.

Election/Restrictions

3. Applicant's election with traverse of Group I (Claims 1-16) in the reply filed on 5/12/08 is acknowledged. The traversal is on the ground(s) that Chakrabarti et al., (Biochem. Biophys. Res. Comm., (1999) 264:871-877) and Dong et al., Blood (2002) 99(8):2637-2646) does not provide direct or indirect nexus between Tel/ETv6 and Stat3 vis-à-vis Stat5 because "these relationships are too tenuous to disclose the role of TEL/Etv6 modulators in modulating Stat3 activities and Stat3-mediated cell proliferation. Therefore the role of TEL/Etv6 in Stat3 activity and Stat3-dependent cell proliferation is a novel and a special technical feature.

This is not found persuasive because the references in combination provide correlative relation between Tel/Etv6 signaling and Stat3 regulation of cell proliferation, which would provide the motivation or incentive to consider the signaling elements as directly interactive. Additionally, at the time of the invention, others in the field had already reported on the nexus or correlation between these cell signaling components, namely, Ho et al., "Fusion of the ets transcription factor TEL to Jak2 results in constitutive Jak-Stat signaling (Blood 93:4354-4364 (1999); cited in the IDS of 4/17/07); Spiekermann et al. "Constitutive activation of Stat3 and Stat5 is induced by leukemic

fusion proteins with protein tyrosine kinase activity and is sufficieint for transformation of hematopoietic precursor cells" (Exp. Hematol. 30:262-271 (2002)); and Nguyen et al., "Tel-Jak2 mediates constitutive activation of the phosphatidylinositol 3'-kinase/protein kinase B signaling pathway" (J.Biol. Chem. 276:32704-32713 (2001); cited in the IDS of 4/17/07). Thus the only conclusion that could reasonably be made by the ordinary artisan is that the technical feature of the invention was well appreciated by others in this field of art prior at the time of invention.

Further, the first presented generic invention in Claim 1 *as interpreted* does not require there being a showing of a direct correlation, only that TEL/Etv6 activity is "indicative" of Stat3 activity (e.g., downstream) and where the claim does not even require a measurement of Stat3 activity as a readout.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 17-26 and 31-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/12/08.

5. Claims 1-16 are all the pending claims under examination.

Information Disclosure Statement

6. The IDS of 5/2/05 has not been considered because copies of the cited references were not provided upon entry of this 371 application to the national stage. Accordingly, the references have been stricken on the attached 1449 form.

7. The IDS of 4/17/07 has been considered and the copy of the examiner's initialed 1449 form is attached. Copies of those references not provided with the filed IDS have been stricken.

Specification

8. The disclosure is objected to because of the following informalities:

a) The amendment to the specification of 5/2/05 to cross-reference the application to related priority documents does not include the relationship to PCT/EP03/12295 (11/4/03) and its priority claim to GB 0225799.6 (8/14/02). Please note that the priority applications cannot be incorporated by reference after the original filing of the instant application. For additional information on claiming benefit to an earlier filed application see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

b) The use of a trademark, e.g., GeneChips™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicants are requested to carefully check the entire specification for any other trademarks that may not be properly identified.

Appropriate correction is required.

Claim Objections

9. Claims 10 and 16 are objected to because of the following informalities:

a) Claim 10 recites “the test compound” where in depending from Claim 1, would seemingly be more consistent if recited as “the compound.”

b) Claim 16 recites in the last line "can be observed as a reduction of reporter gene expression". The claim might include a reference to the reporter gene expression being from the reporter gene construct. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-9 and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims1-5 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step of identifying the modulating effect of the test compound selected in step iii) of Claim 1 on Stat3-dependent cell proliferation.

b) Claims 6-9, 11-13, 15 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a) the nexus between the binding agent, TEL/Etv6 and Stat3 in Claim 6, b) the step of identifying the modulating effect of the test compound selected in step ii) of Claim 6 on Stat3-dependent cell proliferation and c) the nexus for reporter gene expression upon contact between TEL/Etv6 and the binding partner to Stat3-dependent cell proliferation in Claim 16.

c) Claim 2 is indefinite for the recitation "said agent is effective in enhancing cytokine-induced inhibition of cell proliferation" because the recitation is broader than the generic method of Claim 1 for determining that the test compound is an agent effective in modulating Stat3-dependent cell proliferation. Alternatively, what is the correlation between Stat3-dependent and cytokine-dependent cell proliferation?

d) Claim 7 is indefinite for the recitation "wherein the variant or fragment of TEL/Etv6 has the ability to bind Stat3" because this means the variant or fragments of TEL/Etv6 can bind to the generic binding partner of claim 6 and to Stat3 of Claim 7. Full length TEL/Etv6 is not defined as being a binding partner for Stat3 in the method. Claim

14 describes there to be a physical association between TEL/Etv6 and Stat3 which does not require binding per se. Thus the relationship of TEL/Etv6 binding to Stat3 requires clarification for the method.

e) Claim 13 recites the limitation "the substance". There is insufficient antecedent basis for this limitation in the claim. The preceding claims all recite "test compound."

f) Claim13 is indefinite for the recitation "confirming the substance inhibits cell proliferation of a cytokine-sensitive cancer" because the recitation is broader than the generic method of Claim 6 for determining that the test compound is an agent effective in modulating Stat3-dependent cell proliferation. Alternatively, what is the correlation between Stat3-dependent and cytokine-dependent cell proliferation?

g) Claim 16 is indefinite for the recitation in element (ii) "identifying substances which inhibit said interaction in said cell" because the recitation does not describe the relationship between the identified substance and the test compounds in the preceding step.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

11. Claims 15 and 16 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

It is unclear if a cell or cell line expressing a TEL/Etv6 variant or a fragment thereof which has the ability to interact with any binding partner much less Stat3 is known and publicly available, or can be reproducibly isolated without undue experimentation. The specification teaches constructs for TEL mutants: TELΔ41-127 (i.e. AP), TELΔ122-176, TELΔ122-217, TELΔ268-333, TELΔ303-333, TELΔ333-352, TELΔ442-452, TELDBDM (R396K; R399K) that are transfected into "Stat3-ER-A375 cells and HEK 293 cells" (p. 36, ¶3-4). Otherwise, Applicants have not demonstrated or disclosed the existence of any natural or wild-type cell or cell line that meets the requirements of Claims 15 and 16.

Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; and/or (2) a cell line which expresses a TEL/Etv6 variant or a fragment thereof which has the ability to interact with any binding partner claimed is an unpredictable event.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International

Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Enablement

12. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for screening agents that modulate TEL-mediated repression of Stat3 transcriptional activity from a Stat3-ER reporter construct and/or that modulate TEL binding to Stat3 in cytokine-responsive tumor cell lines (e.g., TEL/Etv6 binding directly to Stat3 in association with mSin3A, NcoR and SMRT in a co-repressor complex as demonstrated in the A375 cells and HEK 293 cell lines in response to IL-6 family-cytokine stimulation), does not reasonably provide enablement for correlating the

modulation of any TEL activity or the binding of TEL to any binding partner in the presence of any test agent, to where the agent modulates Stat3-dependent cell proliferation in any cell or cell line. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 1-5 and 10 are *interpreted* as being drawn to a method for identifying modulating agents for Stat3-dependent proliferation and where the agent is selected on the basis of the steps comprising incubating TEL/Etv6 and a compound, detecting TEL/Etv6 modulation in the presence and the absence of the compound in order to compare whether there is an alteration in the TEL/Etv6 activity, where the alteration in activity by the compound indicates that it would be an effective modulator of Stat3-dependent cell proliferation (Claim 1), where modulation of TEL is measured as inhibition of its activity and the agent enhances cytokine-induced inhibition of cell proliferation (Claim 2), where modulation of TEL is measured as activation of its activity

and the agent inhibits Stat3-expressing cell proliferation and Stat3 is phosphorylated (Claim 3), where cell proliferation in Claim 3 is ras-independent (Claim 4), where cell proliferation is for a melanoma or carcinoma (Claim 5), and the method further comprises determining whether the compound modulates Stat3-dependent cell proliferation (Claim 10).

Claims 6-9 and 11-16 are *interpreted* as being drawn to a method for identifying modulating agents for Stat3-dependent proliferation and where the agent is selected on the basis of the steps comprising incubating TEL/Etv6 or a variant or fragment thereof, a binding partner and a test compound and determining whether in the presence or absence of the test compound a change or modulation for the interaction between the TEL/Etv6 protein and the binding partner occurs (Claim 6), where the variant or fragment of TEL/Etv6 binds Stat3 (Claim 7), where the fragment of Claim 7 is between 50 and 350 amino acids in length (Claim 8), where the binding partner of Claim 6 is Stat3, a variant or fragment thereof (Claim 9), the TEL/Evt6 polypeptide or binding partner of Claim 6 is labeled with a detectable label and the other is immobilized on a solid support (Claim 11), where the modulation in Claim 6 involves inhibiting the interaction (Claim 12), where the method of claim 12 confirms that the test compound inhibits proliferation of a cytokine-sensitive cancer (Claim 13), where the test compound of Claim 12 is examined for whether it inhibits the physical association between TEL/Etv6 and Stat3 (Claim 14), where the method of Claim 6 further comprises contacting a test compound with a cell expressing the TEL/Etv6 polypeptides which can interact with the binding partner and identifying compounds that inhibit the interaction

between the TEL/Etv6 polypeptide and the binding partner in the cell (Claim 15), and where the method of Claim 15 comprises a cell expressing the TEL/Etv6 polypeptide, the binding partner and a reporter gene construct and contacting the cell with a test compound in order to inhibit binding between TEL/Etv6 polypeptide and the binding partner and where the inhibition is observed by a reduction in reporter gene expression (Claim 16).

The relative skill in the art for practicing the method is a skilled technician in a high throughput drug screening lab with a background in second messenger signaling mechanisms relating to gene transcription in cell proliferation.

Disclosure in the Specification/ Undue Experimentation

The following working embodiments are disclosed and accordingly are enabling for the scope of a method drawn to the steps described in each of the examples:

Example 6: The specification describes an experiment were performed to investigate the function of TEL in Stat3-mediated inhibition of cell proliferation essentially as described in Example 4 but using TEL siRNA nt 540-560, 5'-CCCUCCCACCAUUGAACUGdTdT-3' (SEQ ID NO:4) and 5'-CAGUUCA AUGGUGGGAGGGdTdT-3' (SEQ ID NO:5). This Example follows cell proliferation of Stat3-ER-expressing A375 cells treated with 4HT or a combination of 4HT and OSM, and in the absence or in the presence of siRNA to TEL. The specification states “TEL was strongly increased upon 4HT or 4HT/OSM treatment. This increase was largely prevented in the presence of TEL siRNA. Surprisingly, in the presence of TEL siRNA, Stat3-mediated inhibition of A375 cell proliferation was significantly increased (from

about 28% to about 40%). Stat3-dependent transcription of luciferase, induced by 4HT or OSM, was significantly increased (from about 6 to 16 fold increase over control, and from about 9 fold to 18 fold increase over control respectively) when TEL expression was reduced by siRNA." The specification states "the inhibition of breast carcinoma and melanoma cell proliferation by IL-6-type cytokines, as exemplified here with A375 cells, is dependent on Stat3 activity, which can be induced by reducing TEL activity." **No data from this experiment are shown in the application as filed.**

Example 7: The specification describes an experiment in which TEL- or control, pcDNA3.1-transfected Stat3ERA375 cells, treated with 4HT were cultured in the presence or absence of Trichostatin A (TSA; 250 nM), a general HDAC inhibitor. Addition of TSA to 4HT-stimulated cells prevented the repression of Stat3 activity by TEL, but had no effects on Stat3 mediated transcriptional activity in pcDNA3.1-transfected cells. **No data from this experiment are shown in the application as filed.**

Example 8: The specification describes an experiment in which Stat3-ER-A375 cells and HEK 293 cells were transfected with the different TEL mutants, a Stat3 reporter plasmid and a Renilla plasmid. Cells were treated with 4HT or OSM for 24 h and luciferase activity was measured using the luciferase assay described in Example 1. Only TEL .DELTA.P, missing the pointed domain, failed to repress Stat3 activity. TEL delta 333-452 represses Stat3 activity, whereas TEL delta 442-452 is not able to repress Stat3 activity. TEL, TEL delta P, TEL delta 333-452 and to a less extent TEL

delta 442-452 still interact with Stat3. **No data from this experiment are shown in the application as filed.**

Example 9: The specification describes an experiment in which extracts from nuclear-enriched fractions were prepared from control or OSM-stimulated A375 cells. Antibody probing nuclear lysates reveals the expected increase in Stat3 levels following OSM treatment, while the nuclear content of TEL is not affected by OSM. Endogenous TEL was present in Stat3 immunoprecipitates and the levels of TEL associating with Stat3 increased in OSM-treated compared to control-treated nuclear extracts. Conversely, Stat3 is present in a TEL-containing complex, pulled down through an immobilized GGM-containing oligonucleotide, which is a binding site for TEL. **No data from this experiment are shown.**

The conclusions that Applicants draw from these studies are that TEL is a transcriptional repressor of Stat3 transcriptional activity by interacting with Stat3 directly and recruiting HDACs to the Stat3 transcriptional complex.

Notably, in order to have fully evaluated the disclosure, the examiner was required to resort to the post-filing date publication by the inventors (Schick et al. (J. Biol. Chem. 279(37):38787-38796 (2004); cited in the IDS of 4/17/07) showing these same data in table and figure format.

The examiner's position is that the specification demonstrates TEL acts as a repressor or negative regulator of Stat3 transcriptional activity and whose repressor activity is further dependent on recruitment of a co-repressor complex, comprising mSin3A, NcoR and SMRT, which are known to interact with histone deacetylases

(HDACs) [0127]. Thus it is not predictable that the binding of TEL alone to Stat3 would inhibit Stat3 transcriptional activity, or that any test compound could inhibit this interaction to modulate Stat3 transcriptional activity measured by cell proliferation.

Applicants have demonstrated with a single compound, Trichostatin A, that TEL repressor activity for Stat3-mediated transcriptional activity could be blocked in the A375 cell line. Applicants have demonstrated TEL repressor activity for Stat3 transcriptional activity in a transfected cell line A375 carrying a Stat3_ER reporter construct and in the HEK 293 cell line.

Applicants have not demonstrated the universality of Stat3 regulation of cell proliferation in any cell much less any cancer cell. Applicants have not demonstrated the universality for the repressor activity of TEL for Stat3 transcriptional activity in any cell line much less any cancer cell line. Applicants have not demonstrated that TEL/ETv6 has the universe of binding partner(s) encompassed by the claims. Thus the specification is not enabling for screening drugs where modulation or alteration of any TEL activity is correlative with modulating Stat3-dependent cell proliferation in any cell much less any cancer cell.

The ordinary artisan would be required to perform undue experimentation in order to identify the universe of TEL/Etv6 activities and the universe of TEL/Etv6 binding partners encompassed by the claims to practice the method scope in assessing whether the universe of test agents/test compounds would positively or negatively affect any TEL/ETv6 activity or binding property to then correlate this change with Stat3-dependent cell proliferation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 1, 2, 5, 6-10 and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakrabarti et al., (Biochem. Biophys. Res. Comm., (1999) 264:871-877; cited in the IDS of 4/17/07) in view of Dong et al., Blood (2002) 99(8):2637-2646; cited in the PTO 892 form of 4/10/08) and further in view of Kortylewski et al. (Oncogene 18:3742-3753 (1999); cited in the IDS of 4/17/07).

Claims 1, 2, 5 and 10 are *interpreted* as being drawn to a method for identifying modulating agents for Stat3-dependent proliferation and where the agent is selected on the basis of the steps comprising incubating TEL/Etv6 and a compound, detecting TEL/Etv6 modulation in the presence and the absence of the compound in order to compare whether there is an alteration in the TEL/Etv6 activity, where the alteration in activity by the compound indicates that it would be an effective modulator of Stat3-

dependent cell proliferation (Claim 1), where modulation of TEL is measured as inhibition of its activity and the agent enhances cytokine-induced inhibition of cell proliferation (Claim 2), where cell proliferation is for a melanoma or carcinoma (Claim 5), and the method further comprises determining whether the compound modulates Stat3-dependent cell proliferation (Claim 10).

Claims 6-9 and 12-16 are *interpreted* as being drawn to a method for identifying modulating agents for Stat3-dependent proliferation and where the agent is selected on the basis of the steps comprising incubating TEL/Etv6 or a variant or fragment thereof, a binding partner and a test compound and determining whether in the presence or absence of the test compound a change or modulation for the interaction between the TEL/Etv6 protein and the binding partner occurs (Claim 6), where the variant or fragment of TEL/Etv6 binds Stat3 (Claim 7), where the fragment of Claim 7 is between 50 and 350 amino acids in length (Claim 8), where the binding partner of Claim 6 is Stat3, a variant or fragment thereof (Claim 9), where the modulation in Claim 6 involves inhibiting the interaction (Claim 12), where the method of claim 12 confirms that the test compound inhibits proliferation of a cytokine-sensitive cancer (Claim 13), where the test compound of Claim 12 is examined for whether it inhibits the physical association between TEL/Etv6 and Stat3 (Claim 14), where the method of Claim 6 further comprises contacting a test compound with a cell expressing the TEL/Etv6 polypeptides which can interact with the binding partner and identifying compounds that inhibit the interaction between the TEL/Etv6 polypeptide and the binding partner in the cell (Claim 15), and where the method of Claim 15 comprises a cell expressing the TEL/Etv6 polypeptide,

the binding partner and a reporter gene construct and contacting the cell with a test compound in order to inhibit binding between TEL/Etv6 polypeptide and the binding partner and where the inhibition is observed by a reduction in reporter gene expression (Claim 16).

The claimed method inventions were prima facie obvious at the time of the invention over Chakrabarti, Dong and Kortylewski.

Chakrabarti discloses TEL is a DNA-binding, transcriptional repressor which involves the recruitment of a repressor complex including SMART, SIN3A, N-CoR and which is further mediated through histone deacetylases. When the histone deacetylase inhibitor, TSA, is added to the mix in a reporter gene assay using yeast transcription activator Gal4 in NIH-3T3 or COS7 cells, repression by TEL and truncation variants thereof were inhibited by TSA. The results show TEL recruits components of a repressor complex at the promoter site and such complexes are postulated for other transcription factors which interact with co-repressors. Chakrabarti discloses that the activity described for TEL could be a common mechanism of alteration of gene transcription leading to neoplastic transformation and cancer.

Dong examined the transcriptional activity for Stat3 using Stat3 reporter gene constructs and found that SMRT and CoR are recruited with Stat5 for regulating Stat3 activity.

Kortylewski teaches that members of the IL-6 family of cytokines including IL-6, OSM, LIF and CNF have been shown to inhibit proliferation of some leukemia, melanoma, prostate and breast cancer cells and this inhibition is mediated by Stat3, and

that in some cellular contexts, Stat3 has anti-proliferative and anti-oncogenic effects. Kortylewski teaches with receptor chimeras and dominant negative forms of Stats that growth-arrest of human A374 melanoma cells depends on Stat3.

One skilled in the art would have been motivated and been reasonably assured of success in having produced a method for screening drugs that modulate Stat3 dependent growth by measuring the drug effect on TEL/Etv6 activity at the time of the invention over Chakrabarti, Dong and Kortylewski. Chakrabarti and Dong establish the nexus between Stat3 and TEL as comprising or sharing SMRT and Co-R, where TEL in combination with these co-factors had been recognized as having repressor function in transcription activity for many different genes and the potential role in regulating cell proliferation, and Dong shows that Stat3 transcriptional activity is affected by SMRT and Co-R in reporter gene assays with Stat5. Dong appreciates that Stat3 has been shown in some signaling pathways as being an oncogene whereas under other conditions is anti-oncogenic, and Kortylewski teaches and appreciates the anti-oncogenic effect of the IL-6 family of cytokines mediating the down-regulation of cell proliferation thru Stat3. Because it was known that TEL was a repressor of transcriptional activity for many genes and regulation of Stat3 activity was possible because of the shared co-factors between TEL and Stat5, one skilled in the art would have been motivated to have formulated a method assay for screening drugs that modulated the activity of TEL (or its binding with SMRT or Co-R) in order to modulate the activity of Stat3 because of the motivation provided in the references to identify mechanisms for regulating cytokine-mediated cell proliferation which affect Stat3. One skilled in the art would have been

reasonably assured of success in practicing the method assay because of the availability of the reagents, reporter gene constructs, variants for TEL, variants for Stat3 and the nexus between the cytokine-mediated downregulation of cell prolfiferation occurred thru Stat3 and TEL being a negative repressor for transcpriotnal activity for many genes involved in transformation and oncogenesis. The method inventions were prima facie obvious over Chakrabarti, Dong and Kortylewski.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Partial Signatory Authority